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Reply to the Editor:

We are grateful to Dr Catalana-Lopez for his continued comments regarding our work.

Although we do not want to prolong unnecessarily this correspondence, a couple of points are worthy of note in his response.

First, the suggestion of including observational evidence in the meta-analysis is flawed, and we found ourselves in this position. As Rosenbaum and Rubin,[1] the propensity score methods used by the authors can only address confounding when case mix adjustment is possible to the extent that the prescriber's decision to prescribe a treatment is otherwise ignorable. This is clearly not the case in our situation, in which the observational studies describe a substantial latency (unmeasurable bias) associated with the decision to prescribe, which has been incorrectly interpreted as a risk associated with aprotonin.[2,3] Thus, following Dr Catalana-Lopez's advice in this situation would actually compound the previous errors of interpretation that have led us to our difficulties with this agent.

Second, Dr Catalana-Lopez is simply incorrect when he suggests that network meta-analyses have the same status as observational studies. Network meta-analyses preserve the original randomization in trials, and provide fully conditional estimates of treatment effect. However, network meta-analyses require an additional assumption (of exchangeability; ie, that subjects share characteristics from the overall population and may, thus, appear in any of the trials). Thus, rather than fully giving up the protection of randomization, we may consider network meta-analyses to be quasi-randomized estimates.

Finally, with regard to potential conflicts of interest, they should be declared upfront and leave the reader to decide of their importance. These authors take conflicts of interest seriously and, as indicated by Dr Catalana-Lopez, have declared all possible conflicts in accordance with required journal requirements.

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GENDER DISPARITY MAY CONTRIBUTE TO THE QUASI PRESERVATION OF CARDIOPROTECTION BY REMOTE PRECONDITIONING WITH ISOFLURANE BUT NOT PROPOFOL IN CABG

To the Editor:

We read with great interest the article by Kottenberg and colleagues[1] published online in *The Journal of Thoracic and Cardiovascular Surgery* on March 1, 2013. They have done a series of impressive translational works to explore the underlying mechanisms of cardioprotection by remote ischemic preconditioning (RIPC) with isoflurane or propofol in patients undergoing coronary artery bypass grafting (CABG).[1-3] In their fundamental study published in *Acta Anaesthesiologica Scandinavica*,[2] they designed 2 independent substudies and found that isoflurane may be more effective in the preservation of cardioprotection by RIPC than propofol. Then, based on 2 consequently separated and independent studies,[2,3] they believed that differential activation of signal transducer and activator of transcription 5 (STAT 5) phosphorylation may be the contributing factor.

Nevertheless, there remains inconclusive information about this interesting issue when looking into the fundamental study. In that study,[2] the male proportion may be even within the substudy (RIPC vs control with isoflurane; RIPC vs control with propofol); however, it may be uneven between the 2 substudies (isoflurane vs propofol, 89.7% vs 75.8%; mean difference, 14%).

Accumulating evidence from animal studies has supported gender-specific cardioprotection by ischemic